

THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES
SEPTEMBER, 1911

ORIGINAL ARTICLES

IS THERE SPECIFIC TREATMENT FOR DIABETES MELLITUS?¹

By HENRY SEWALL, PH.D., M.D.,

PROFESSOR OF MEDICINE IN THE UNIVERSITY OF COLORADO, DENVER.

PRELIMINARY CONSIDERATIONS.

VAST as has become the accumulation of literature on diabetes mellitus, it is obvious that real advance in the knowledge of the disease demands still more facts. Though the observations to be detailed failed to sustain toward their conclusion the brilliant promise of therapeutic efficiency which rewarded the treatment of certain cases at the outset, it seems possible that the very failures may have value in the conception of an efficient working hypothesis.

Carbohydrates enter the stomach under a variety of complex chemical forms, but in the process of digestion and absorption they are transmuted chiefly to the relatively simple product, grape sugar or dextrose ($C_6H_{12}O_6$). When retained in the tissues, the soluble sugar appears to be reduced to a less soluble starch (glycogen), which is again converted into sugar preliminary to utilization. Sugar is said to occur normally in the human blood in a concentration of about 1 part to 1000. So essential to the metabolism of protoplasm is the carbohydrate molecule, that when this substance is not available, other foodstuffs, proteids and perhaps fats, undergo chemical transformations by which carbohydrate radicles are offered to the tissues. Whenever the proportion of sugar in the blood rises above 2 in 1000, the impermeability of the kidneys is

¹ Read before the Association of American Physicians, May 10, 1911.
VOL. 142, NO. 3.—SEPTEMBER, 1911.

overcome, dextrose passes through, and the result is glycosuria. Glycosuria is, as a rule, simply an expression of excessive concentration of sugar in the blood. The wonderful power possessed by the normal tissues of appropriating carbohydrate so as to prevent its accumulation in the circulation may be overcome experimentally by giving excessive amounts of sugar in the food. It is obvious that the physiological machinery which coördinates the metabolic activity of every living molecule with the varying supply of carbohydrate in the ration so as to provide working material for the cells while preventing an excess of sugar in the blood must be a mechanism of extraordinary complexity. *A priori*, it seems probable that lapses of efficiency in one or another part of this nutritive machinery should occasionally occur leading to a temporary glycosuria without implying any serious departure from the normal. It is also to be expected that the mechanism for carbohydrate metabolism should at times suffer from permanent defects in one or another of its parts, resulting in a more or less unmanageable tendency to the accumulation of sugar in the blood, thus giving rise to the pathological state known as diabetes mellitus. As the disorders leading to glycosuria demand for their explanation a knowledge of the normal carbohydrate metabolism of the body, diabetes is the one disease a discussion of which is attempted in every text-book on physiology. The *rationale* of the carbohydrate mechanism is made somewhat clearer by a consideration of the parallel system for the utilization of oxygen in the body. We know that the complex machinery of respiration subserves one prime double purpose, and is under the domination of one double force—the hunger of the tissues for oxygen and their intolerance of an excess of carbonic acid.

Adequate oxidation of the tissues and removal of carbonic acid presupposes the efficient coöperation of a great number of physiological events, such as the rhythmic discharge of the respiratory centre, normal elasticity of the lungs, and diffusion attributes of the air cells, sufficient contractile power of the heart and blood-vessels, and oxygen conveying power of the red corpuscles. These and many other functions regulate the procession of oxygen and carbonic acid through the body. When this process is acutely interfered with the physiological reaction is hyperpnea, in which group after group of muscles not ordinarily employed in respiration are set in action in the endeavor to satisfy the oxygen hunger of the tissues and abolish the irritation of the waste product. In an analogous way the whole metabolism of the body may be modified in diabetes in a desperate effort to give the tissues the sugar food they are denied. From a practical therapeutic standpoint our comparison is of further significance, for every physician knows that the efficient treatment of disturbances of tissue oxidation depends upon discovery of the specific erring function out of many which

may be at fault. In a similar way it is possible that the disease resulting in glycosuria may be indifferently produced by manifold different functional failures, and, as in the case of the respiratory dyscrasia, an efficient treatment can only be devised which shall correct the particular physiological function in fault. Such a conclusion brings bewildering complexity into the practical consideration of diabetes.

As the phenomena of respiration are essentially under the control of tissue metabolism, so it has become equally clear that carbohydrate in the body fulfils its function only in the molecules of the living tissue, and that the coördinate action of a considerable number of individual organs and their products is necessary to pilot the sugar absorbed through the complex route leading to its oxidation and excretion. When Claude Bernard, in 1849, produced glycosuria in a rabbit by his "pique" experiment, puncture in a certain area of the floor of the fourth ventricle, it seemed as though the equilibrium of carbohydrate metabolism depended upon a balance between the nervous system and the liver protoplasm, for the glycosuria in question did not occur if the store of glycogen normally present in the liver was removed by starvation before the performance of the pique. When Minkowski and von Mering, in 1889, showed that a severe and fatal form of diabetes followed the ablation of the pancreas from animals, it led to the demonstration that the pancreas furnishes to the body an internal secretion which is absolutely necessary to normal carbohydrate metabolism. Through Opie and others it has been rendered probable that this secretion is formed in the pancreas in the islands of Langerhans. The fact that extract of the adrenal body when injected into animals causes glycemia and glycosuria, and that extracts of adrenal body and pancreas mixed *in vitro* neutralize each other, led Zuelzer² to generalize the conclusion that the adrenal bodies and the pancreas play the part of physiological antagonists in carbohydrate metabolism, the former tending to mobilize the molecules into diffusible sugar and the latter to fix them in a more stable form in the tissues. Eppinger, Falta, and Rudinger³ have carried on important researches upon the relations in carbohydrate metabolism of the internal secretions of the adrenals, the thyroid, the parathyroids (and chromaffin system), and the pancreas, in which it is made clear that mobilization or fixation of sugar depends more or less upon a balance between the activities of these glands. The pancreas and the thyroid, and the pancreas and the adrenals, intensely inhibit one another, while the thyroid and the adrenals are mutually stimulant in the production of glycemia. These authors made laborious determinations of the metabolism in dogs before and

² Deutsch. med. Woch., 1908, No. 32, S. 1380.

³ Ueber die Wechselwirkungen der Drüsen mit innerer Sekretion, Zeitschr. f. klin. Med., 1908, 1909, etc.

after the extirpation of various glands of internal secretion. They found, for example, that in pancreas-free dogs at the height of metabolic disturbance the injection of adrenalin causes enormous increase of sugar and nitrogen elimination; whereas, like treatment in thyroid-free dogs caused no glycosuria. They hold that the glycosuria following piqure is due to a liberation of adrenal internal secretion. They conclude that while genuine diabetes has its origin in profound disturbances of equilibrium between the glandular organs regulating metabolism, the final cause of the disease remains in deepest obscurity.

Pflüger, the physiologist, in disputing the evidences for an internal secretion by the pancreas, found by experiments on frogs an important nervous connection between the duodenum and the pancreas.⁴

Severing these nerves leads to glycosuria. It is concluded that the duodenum is a peripheral regulating organ for sugar mobilization and an inhibitor of sugar formation.

Minkowski failed to confirm these results on mammals.

Pflüger holds that a nerve centre in the medulla controls the formation of diastase in the liver, and consequently regulates the rate of sugar production.

Cushing and others have shown that removal of the anterior lobe of the pituitary body is followed by metabolic disturbances in which glycosuria is one result.⁵

The ductless glands operate by internal secretions, which are absorbed by the circulation. The active agents in the secretions are known as "hormones," which "Starling defines as chemical messengers, which, formed in one organ, travel in the blood stream to other organs of the body and effect correlation between the activities of the organ of origin and the other organs on which they exert their specific effect. Such substances belong to the crystalloid rather than the colloid class; they therefore are thermostable, and do not act as antigens when injected into the animal."

In an admirable review of the subject, Howell⁶ points out that the hormone may act at least in two ways—either as a chemical stimulus, illustrated in the excitement of pancreatic secretion under the influence of secretin, or as an activator, in which role it simply develops some latent property of a chemical body, as by turning an inert proferment into an active ferment; according to Howell, "This at least would seem to be true for the hormone, of unknown nature, given off by the pancreas and concerned in the glycolysis of sugar in the organism."

However numerous may be the physiological defects which lead

⁴ Quoted from Blumenthal, *Deutsch. med. Woch.*, October 22, 1908.

⁵ *Johns Hopkins Hosp. Bull.*, May, 1910.

⁶ *The Chemical Regulation of the Processes of the Body by Means of Activators, Kinases, and Hormones*, Science, 1910, xxxi, 93.

to glycosuria, we must believe that the fundamental nature of diabetes depends upon a disorder of tissue metabolism. As Halliburton puts it, "The difficulty in diabetes probably lies in an impairment of the capacity of the cells of the body to prepare the sugar for oxidation. In this process the sugar, or its early oxidation product, called glycuronic acid, is split into smaller molecules and ultimately leaves the body as carbonic acid and water."⁷

The current of modern observation, experiment, and speculation sets powerfully toward the conclusion that practically all the functions that we have been accustomed to define as the criteria of life in matter are carried on by protoplasm through the agency of quasi-adventitious radicles, which may join or separate from the protoplasm without altering its integrity. These radicles are known as ferments, or enzymes, for it is their fundamental peculiarity that they may cause a rearrangement of contiguous molecules without themselves being disorganized. They are essential agents in metabolism, whether of building up or breaking down. According to the view of Adami,⁸ the enzyme radicle is not to be considered as a distinct molecular side chain of the cell, but rather that specific enzyme actions are a constitutional property of the living proteid molecule. There seem to be various orders of these intermediaries through which the reactions of living matter are invoked.

A conservative and accurate physiologist (Langley) maintains that the contraction of the skeletal muscle is not induced by the direct action of the motor nerve impulse, but indirectly through "receptive substances," which are interpolated between the nerve endings and the muscle, and which are not an integral part of the protoplasm, but are more or less intimately connected with it. Various drugs exert their effects by combining with the receptive substance. He believes that "nerve impulses can only cause contraction by acting on a receptive substance. . . . Curari, in combining with the receptive substances, simply prevents them (and so the contractile substance) from being influenced by nerve stimuli."⁹

It will, of course, occur to every one that the chief modern theory of immunity is founded on the assumption that a molecular intermediary, an adventitious side chain, correlates the reactions of tissue cell with the antigen.

That the muscle substance contains a glycolytic ferment has been established by a number of experimenters, and recently Ransom confirmed these results with the conclusion that, "It is possible to prepare from frozen muscle a plasma containing a ferment or ferments capable of converting glucose or glycogen into lactic acid, CO₂, and alcohol."¹⁰

⁷ Diabetes Mellitus from the Physiological Standpoint, Practitioner, July, 1907, p. 1.

⁸ Principles of Pathology, 2d Ed., i, 70 to 84.

⁹ Jour. Physiol., 1909, xxxix, 236.

¹⁰ A Contribution to the Study of Muscle Enzymes, Jour. Physiol., 1910, xl, 1.

The first important work in this direction was that of O. Cohnheim.¹¹ This author found that solutions of dextrose added to an extract of pancreas remained unchanged. A nearly equally negative result attended the mixture of dextrose with the expressed juice of muscle. But when muscle juice was added to the extract of pancreas, the mixture developed marked glycolytic powers, and considerable amounts of sugar added to it were destroyed. As this reaction occurred in a homogeneous, cell-free fluid, it must have been due to a ferment. The active substance of the pancreas withstood boiling and dissolved in alcohol, and therein resembles the active principles of the internal secretions of the adrenals and the thyroid rather than the class of ferments. It was found that the glycolytic power of the muscle-pancreas mixture was annulled by adding an excess of the pancreatic constituent. The maximum glycolytic effect was obtained when 75 grams of muscle was combined with about 0.8 gram of pancreas. Cohnheim's experiments have been repeated by a number of experimenters, some of whom have confirmed and others failed to obtain his results. To this latter group belongs Simpson,¹² a late worker on the subject.

Still more recently P. A. Levene and G. M. Meyer have submitted the problem to renewed investigation, and seem to have resolved much of its obscurity. They found, like Cohnheim, that a solution of glucose lost much of its reducing power when digested with a muscle-pancreas mixture. Nevertheless, this result does not indicate, as had been assumed, loss of sugar by oxidation, but rather a concentration of the carbohydrate molecules into osazones, which do not respond to the cupric reduction test.¹³

Building on these ideas, Zuelzer attacked the clinical problem of diabetic therapeutics.¹⁴ He discovered that in animals made glycosuric by the exhibition of adrenalin the urine became sugar-free after the intravenous injection of an extract of pancreas. He concluded that there exists a physiological antagonism between the adrenal and the pancreatic hormones, and that diabetes was the result of the balance of power turning in favor of the former. By a method whose details are not disclosed, he made extracts from the pancreatic glands obtained from living animals at the height of digestion. In several severe cases of human diabetes, he made intravenous injections of this pancreatic extract, with the result of causing the sugar to disappear from the urine for three or four days. The patients usually suffered from a severe chill following the treatment.

W. M. Croftan describes a severe case of juvenile diabetes in which

¹¹ Hoppe-Seyler's Zeitschr. f. Physiol. Chemie, 1903, S. 336; 1904, S. 401; 1906, S. 253.

¹² Biochem. Jour., 1910, v. 126.

¹³ On the Combined Action of Muscle Plasma and Pancreas Extract on Glucose and Maltose, Jour. Biolog. Chem., April, 1911, p. 96.

¹⁴ Zeitschr. f. Exp. Path. u. Therapie, 1908-09, Band v, S. 307.

favorable results followed the administration by mouth of dried pancreas in capsules, followed by capsules of secretin.¹⁵ Later, he reports success in the administration of a commercial extract of pancreas.¹⁶

At an earlier date A. C. Croftan¹⁷ found great diminution of sugar excretion in diabetic patients to whom he administered a mixture of expressed muscle juice and pancreatic extract. As no further results are reported, we must conclude that later trials were unsuccessful.

ORIGINAL WORK.

My own interest in the study of diabetes mellitus was but general in character until a little patient, a girl, aged seven years, under my care, was found to have a glycosuria which, at first manifested only in the morning urine and amenable to regulation of the diet, later became constant and unmanageable. In despair, a mode of treatment was adopted which was formulated on theoretical considerations. For a time the results were so definite and happy that I was encouraged to pursue the general plan of treatment in other cases. The therapeutic outcome in certain subjects has been of such a character as to warrant a record of the observations. These studies have been greatly extended through the cordial coöperation of certain professional colleagues, in particular Dr. Moses Kleiner and Dr. S. Ringolsky, who enjoy an exceptional clinical experience with diabetes mellitus.

At this place, also, may be expressed my deep obligations to Professor J. C. Todd, of the University of Colorado, for many scores of estimations of urea and ammonia in the urines of my patients. Cordial thanks for advice or assistance is also due to Professor W. D. Engle, of the University of Denver; Dr. P. L. Leyda, of the County Hospital, and to Dr. R. T. Woodyatt, of Rush Medical College.

THE THERAPEUTIC EFFECTS OF MUSCLE INFUSIONS IN DIABETES MELLITUS.

In reflecting on the physiological errors involved in the establishment of diabetes, it seemed to me probable that one vital link in the pathology consisted in the lack or insufficiency of some tissue side chain, receptive body, or enzyme, by means of which the healthy tissue cells are alone enabled to appropriate the sugar in the blood. One naturally turned to the skeletal muscles as offering the principal storehouse of this glycogenic (or glycolytic) tissue

¹⁵ *Lancet*, February 27, 1909, p. 607.

¹⁶ *Dublin Jour. Med. Sci.*, May, 1910, p. 332.

¹⁷ *New York Med. Jour.*, 1904, lxxix, 882.

enzyme. While it might be suspected that such an atomic group would be destroyed if operated on by the digestive apparatus, it is pertinent to recall the statement of Anderson,¹⁸ that sensitization of an animal to a strange proteid is produced by feeding with it.

METHOD OF PREPARING THE BEEF JUICE. One pound of lean beef is ground in a sausage machine and then covered in a jac with a pint of cold water, to which thirty drops of "dilute" hydrochloric acid are added. At times, one quart of water and one dram of acid are used. The mixture stands in the ice box all night, or at room temperature for four hours, and is then strained through cheese-cloth. The liquid should be drunk in the course of the day, one-half to one tumblerful at a time. The meat residue should remain nearly dry and colorless.¹⁹

An excellent device for expressing the juice is made by folding a strong towel once and stitching the ends round two strong sticks. The fabric should be cut so that an oblong bag is made about 11 inches wide by 6 inches deep. The moist beef is placed in this, and the sticks twisted to make pressure.

CASE I (patient of Dr. M. Kleiner, who furnished the following notes).—J. P., male, aged seventy-two years; weight, 190 pounds. Lived in Socorro, N. M. Had suffered from glycosuria for about twenty years. A sister had also suffered from diabetes. He developed diabetic cataract in both eyes during 1908. He was examined by Dr. Kleiner first in December 1909. The patient was then passing 80 to 120 ounces of urine, containing 4 to 6 per cent. of sugar. He was kept on a strict diet until May, 1910, with but slight influence on the sugar excretion. Dr. D. H. Coover refused to operate for cataract, on account of the serious condition of the patient. Dr. Kleiner placed the patient on the acid-beef infusion described above, and in two days all traces of sugar had disappeared from the urine. Dr. Coover removed the cataract from the right eye on May 2, 1910. There was slow healing, without pain or iritis. On May 30, with appropriate glasses, vision in the right eye was normal. The strict diet was discontinued, but the beef juice was partaken of for twenty days after the operation, the glycosuria remaining in abeyance and the general condition of the patient improving in every way. The patient returned to his home in New Mexico, and passed from definite observation. Messages were received at intervals conveying news of his continued well-being until February, 1911, when a relapse was announced. A specimen of urine received at this time had a specific gravity of 1021, and contained a small amount of acetone and about 2 per cent. of sugar.

¹⁸ Anaphylaxis, Johns Hopkins Hosp. Bull., July, 1910, p. 221.

¹⁹ My friend Dr. G. B. Webb has reminded me that this is essentially the beef soup long ago advised by Dr. S. Weir Mitchell in his classic *Fat and Blood* in the treatment of neurasthenic cases. I have frequently employed it with satisfaction in disorders marked by malnutrition, especially tuberculosis.

CASE II (patient of Dr. M. Kleiner).—J. H. H., female, aged fifty-eight years, fairly well nourished. The patient was reckless of any rules of diet. She had had symptoms of diabetes for more than seven years. The urine contained from 3 to 6 per cent. of sugar, 50 to 90 grams in twenty-four hours, and a large amount of acetone. She was frequently prostrated with spells of great muscular weakness. During such an attack the administration of beef infusion was begun early in April, 1910. Within about three days after beginning this treatment the patient recovered her normal strength and energy, which remained with her while the treatment was continued, about two months. The glycosuria and acidosis were unrelieved by the treatment, and in June an attempt was made to improve the patient's metabolism by the administration of pancreatic extract, as in Case VII, but without success. As might have been expected, revulsion against the unpalatable mixtures caused rejection of the whole plan of treatment. The patient went from bad to worse, and died in April, 1911, in diabetic coma, complicated with uremia.

CASE III (patient of Dr. M. Kleiner).—N. H. C., female, aged forty-seven years. On a strict diet, her urine contained 5 per cent. of sugar, and she was losing weight. Beef infusion has been given, at first to the amount of 1 quart; later, 1 pint daily. Now, after three weeks, the patient is gaining weight, she feels much better, and the sugar excretion is reduced to 0.5 per cent., with a diet to which are added daily three slices of toast and a small baked potato.

CASE IV (patient of Dr. M. Kleiner).—J., female, aged sixty-seven years. A bad case, characterized by emaciation, neuritis, and dyspnea. The urine contained a high percentage of sugar, besides albumin and casts. She has taken beef infusion on alternate days for eight weeks. There is improvement as to the pain. The urine is free from sugar, although rice with a teaspoonful of sugar daily is added to the diet.

Dr. Charles G. Duncan, of Socorro, N. M., the family physician of Case I, writes under date of March 31, 1911: "I have used the beef juice in two cases (of diabetes), and have found excellent results. One was a merchant (aged sixty-nine years), in whose urine I found large quantities of sugar. He took the beef juice . . . for two days, then waited two days before commencing again. This was kept up for two weeks, when I could not find a trace of sugar. The other case was a lawyer (aged forty-three years), who had some sugar in his urine, and the results with him were equally as good."

DISCUSSION. It is, of course, unnecessary to dwell upon the well-known fact that the clinical course of diabetes mellitus is at times apparently subject to amelioration under a great variety of

conditions and remedies which probably have no specific relation to the pathological process. It is clear that a much more profound study of the cases which have been presented would be necessary in order to establish the real meaning of the apparent therapeutic effect of the raw-beef infusion. It should be noted that at least the first four cases presented were refractory to ordinary rules of treatment. If further observation should support the hypothesis which led to the treatment—namely, that by such means the body could be furnished with a muscle enzyme capable of metabolizing sugar—an encouraging advance will have been made in the knowledge of diabetes.

Particular attention is called to the age of the half-dozen patients in the foregoing list. All were beyond middle life. Reference will be made later to other subjects, mostly younger in years, in whom little or no success attended the treatment.²⁰

THE USE OF MUSCLE INFUSIONS COMBINED WITH OR FOLLOWED BY WATERY EXTRACTS OF PANCREAS.

Pursuing the same line of argument which holds deficiency of a muscle enzyme responsible for certain cases of diabetes, is but applying current notions of physiology to assume that such an enzyme needs, like the complement of blood plasma, an amboceptor to direct its energies, or, like trypsinogen in the duodenum, an activator such as enterokinase to develop its ferment qualities. We naturally look to the internal secretion of the pancreas to furnish this intermediary body, which may, indeed, play a role quite different to those which have been indicated. In the last few years many attempts have been made to correct the diabetic dyscrasia by the administration of extracts of pancreas, and certain of the results have been very encouraging.

The present article deals with a single instructive case in which for a time there was evidence that extracts of muscle and pancreas played a coördinate action in abolishing glycosuria. That the therapeutic desideratum finally failed itself demands an explanation which is well worth seeking.

CASE VII.—A. S., a girl, aged seven years. Her birth had been premature a month or more. Each year she had suffered an attack of bronchitis in the fall and spring, especially severe when eighteen months old. The child was abnormally bright until the age of four

²⁰ After this paper was in type my attention was led to the brilliant lectures delivered by T. Lauder Brunton nearly forty years ago (*Pathology and Treatment of Diabetes Mellitus*, Brit. Med. Jour., 1874, i, 221). The author not only dwelt upon Schultzen's conception of a glycolytic ferment in the body, but deduced the conclusion that the course of diabetes might be favorably affected by feeding patients with raw beef, so as to supply deficiency in glycolytic muscle enzyme. The therapeutic application was meager and the result disappointing.

and one-half years. She was then greatly frightened, incidental to an operation for the removal of her adenoids, and for more than two years thereafter her mental brightness was less conspicuous. Glycosuria was first detected in March, 1908; she had been more or less invalided with colds all winter. The sugar at first was found only in the specimen of urine passed on rising in the morning. This was true whether the principal meal of the day was taken in the evening or at midday. For some months the glycosuria was controlled by a fairly strict diet containing no sugar and a minimum of starch. In December, 1909, she was prostrated with an infection causing enlargement of the cervical glands and serous inflammation of the middle ears. Thereafter sugar reappeared in the urine, and persisted, at least in the morning specimen, in spite of the strictest diet.

Definite observations were initiated upon the child about this time, in which I had the invaluable assistance of an intelligent mother, with her heart in the work. A rather marked icteroid hue or bronzing of the skin was apt to distinguish periods of glycosuria. The mother frequently remarked that exhibition of the beef infusion (as described below) was immediately followed by an obvious improvement in the child's spirits and brightness, and by a diminution in her abnormal appetite.

The observations in this case included a continuous record of the quantity and specific gravity of the urine secreted, with an estimate by the fermentation test of the sugar eliminated in each twenty-four hours. For a prolonged period, Professor Todd made daily estimations of the amount of urea and ammonia contained in the urine. A mere trace of acetone was constantly present in the urine, the amount apparently varying proportionately with the glycosuria. Only on one day, during an intercurrent attack of bronchitis, was it considerable.

The term "strict diet" embraced such articles as bacon, eggs, butter, cream, cabbage, tomatoes, cauliflower, lettuce, and spinach. When the patient's tolerance for carbohydrates was surpassed through the addition of toasted bread to the strict diet, the carbohydrate was withdrawn as soon as the projected experiment was concluded. Periods of a week or two were allowed to elapse between observations made to test the carbohydrate tolerance of the patient. It is worth noting that the break in carbohydrate tolerance on a given diet was marked first by the appearance of a minute quantity of sugar in the urine, but the amount rapidly increased. For obvious reasons, the observations were cut short in each case without attempting to work out the progress of this glycosuria. That the welfare of the patient did not suffer during this course of experiments is certified by the fact that whereas at the beginning her tolerance for carbohydrates was *nil*, toward the close of the series more than three ounces of bread per diem could be consumed

with impunity. For the sake of brevity, the clinical course of the case will be described merely in outline.

The patient having suffered with persistent glycosuria on a strict diet, on March 20, 1910, was begun, and continued for three weeks, the daily administration of a beef infusion, prepared essentially as described. Under this treatment the twenty-four hours' urine was occasionally free from sugar, but this at once reappeared on the addition of an ounce of bread to the diet. It may be said that with a beef infusion without acid, or in one in which the hydrochloric acid was replaced by an equivalent amount of acetic acid, the results seemed less favorable. On April 15 the daily output of sugar having ranged from *nil* to $\frac{7}{8}$ per cent., one ounce of wheat bread (toasted) was added to the ration. The glucose excretion rose to 9 to 14 grams per diem. On the 19th the acid-beef infusion was resumed, and given daily. The sugar excretion increased to 15 grams on April 22. The simple beef infusion was now abandoned, and in its place was given a mixed beef-pancreas infusion. This was made by soaking about six ounces of ground, fresh beef pancreas in one quart of water acidulated with 1 dram of dilute hydrochloric acid. After standing all night in the ice chest the mixture was strained, and to the fluid was added one pound of ground beef. After remaining four hours at room temperature the mixture was again strained and the juice was consumed by the patient in the course of twenty-four hours. The sugar excretion during the day on which the "mixed" infusion was administered reached 14.67 grams ($\frac{1}{16}$ per cent. of the urine). On the following day, the diet remaining the same and no infusion being given, the sugar excretion fell to less than 7.6 grams, which could easily have been a fortuitous fluctuation. At the beginning of the second day, after exhibition of the mixed infusion, there was begun the administration of a pancreatic infusion. This was made by extracting about one-half pound of ground, fresh beef pancreas with one pint of water acidulated with 30 drops of dilute hydrochloric acid. From the time when the administration of the infusion of pancreas was begun the excretion of sugar ceased. The daily ounce of bread was now removed from the ration, and the urine remained sugar-free without treatment. At the same time there was improvement in the patient's general condition.

It was now important to determine whether the sugar had been driven from the urine by the pancreatic infusion alone or through some relation *in vivo* between the pancreatic infusion and the infusions which had preceded it. Accordingly, on April 28 there was added to the strict diet two ounces of bread. This caused the excretion of about $7\frac{1}{2}$ grams of glucose in the corresponding twenty-four hours. On the following day, under the same diet, a pancreatic infusion was given as before. The amount of sugar excreted rose to more than 16 grams. It was then concluded that an infusion

neither of beef, beef-pancreas, nor pancreas when given alone was capable of abolishing glycosuria, but that they might be effective when given in sequence.

The last member in this sequence was the pancreatic infusion; it was to be determined whether the efficient first member was the simple beef infusion or the mixed beef-pancreas infusion, which, according to Cohnheim, should give rise to a specific compound *in vitro*. The urine of the patient on a strict diet having been sugar-free for some days, on May 15 and for three days following there were added 2 ounces of bread to the ration. Glucose to the amount of nearly 7 grams appeared the first day and rapidly increased to over 16 grams, so that on May 19 the amount of bread was reduced to 1 ounce per diem; nevertheless, the quantity of sugar still increased to over 18 grams. The administration of beef juice on the afternoon of the 19th and morning of the 20th was without effect on the glycosuria. But on the afternoon of the 20th there was given an infusion of pancreas, made by extracting 2 ounces of fresh pancreas with 1 pint of water, and the urine became sugar-free for the following twenty-four hours. Though strict diet was now resumed, a trace of sugar reappeared in the urine for three days; the diminished tolerance probably depended on a lowered resistance involved in an attack of bronchitis, for which the patient was confined to bed, and which, like frequent similar attacks, was possibly an expression of the general metabolic dyscrasia.

Without further treatment, for a period of three weeks following, with the exception of one day, the urine remained completely sugar-free, although the addition of bread to the diet was resumed and the daily amount was increased to as much as 3 ounces, which was the limit of tolerance. It appeared from the last series of observations that an established glycosuria could be abolished by a sequence of beef infusion followed by pancreatic infusion, and that, moreover, the effect of treatment was to greatly increase the range of tolerance for carbohydrates.

It was evidently of great practical moment in the therapeutic régime that an efficient substitute should be found for the fresh pancreas, which is difficult to obtain and most unpalatable. Two preparations were used with this end in view—namely, a proprietary pancreatic powder known as “Holadin,” and a glycerin extract of fresh pancreas. The results were disappointing. It appeared that a glycosuria might be held in check but not abolished by administration of beef infusion followed in some hours by a series of Holadin capsules, representing 10 to 20 grains of the powder. It may be repeated that the general state of well-being of the patient appeared at its best not on the “strict diet,” but when the largest amount of carbohydrate within the limit of tolerance was added thereto.

Renewed tests (June 18 and 25) were now made to verify the

favorable results previously obtained by the administration of a sequence of beef and pancreatic infusions. To my chagrin the treatment was without effect. Tolerance for carbohydrates, which had been overcome by 2 to 3 ounces of bread in the ration, was by no means increased by the treatment. Reflecting on these discordant results, it was surmised that a combination of the beef and pancreas extracts, such as had been used in the first successful experiments, might be necessary in the treatment of glycosuria. This notion was tested early in July. The addition of 3 ounces of bread to the ration caused the appearance of more than 9 grams of glucose in the urine during the same day in which a mixed infusion of beef and pancreas was given. The following day, under the same diet, with the addition of a pancreatic infusion (made by extracting for three hours 3 ounces of fresh pancreas with one pint of water acidulated with 30 drops of dilute hydrochloric acid), the urine became at once sugar-free. Here for the second time a sequence of mixed beef-pancreas infusion followed by pancreatic infusion had abolished the glycosuria.

Continuing the diet containing 3 ounces of bread per diem, sugar again appeared in the urine, but evidently the patient's tolerance had greatly increased, for whereas formerly carbohydrate tolerance had been overcome by much less than 3 ounces of bread, and when once broken the glycosuria had rapidly increased, now 3 to 4 ounces of bread caused the excretion of less than 3 grams of sugar per diem.

The child now (July 15) was placed for a time on strict diet, and the infusion treatment was repeated in preparation for a vacation in the country, where she went in a few days, in excellent condition, enjoying an ounce of bread daily with impunity. While in the country for some two months the diet had included 9 ounces of oatmeal (moist) and 2 gluten wafers daily; but the mother, who had learned to make the Fehling test for sugar, found after a time that the slightest indiscretion in diet was attended with glycosuria.

Very gradually the limits of tolerance became restricted, and in December, 1910, a small amount of sugar appeared even on a strict diet. Treatment with infusions of beef and pancreas was no longer effective. The glycosuria gradually increased, and now in April, 1911, the urine contains not only 30 to 40 grams of glucose per diem, but gives a rather strong reaction for acetone, and for the first time contains a trace of albumin.

Much might be said in the way of discussion on this case, but the results would necessarily be barren for lack of essential data. There was no obvious relation between the amounts of urea and ammonia excreted and the condition as to glycosuria.

There can be no reasonable doubt that the occasional abolishment of glycosuria was a genuine effect of the treatment. It is, of course, open to suspicion that the frequent administration of the beef infusion led to the formation of an antienzyme, yet it is hard

to reconcile such an explanation with the physiology of carnivorous animals. An extract of liver was partaken by the patient on one occasion, and work along this line seems desirable.

The report on a half-dozen other cases of diabetes treated according to the method described may be put in a few words, since the results were practically negative throughout.

CASE VIII (patient of Dr. S. Ringolsky).—M., female, aged forty-one years. Had manifested occasional glycosuria since the age of twenty years. Any nervous excitement or overstrain increased the condition. The pleasant relaxation of a vacation would greatly increase her tolerance for carbohydrates. Sugar appeared in the urine when 4 to 5 ounces of bread were added to the diet, and the quantity was not decreased for the few days while the treatment was pursued.

CASE IX (patient of Dr. Ringolsky).—W., female, aged about forty-eight years. Sister of the above. On a general diet she had excreted upward of 70 grams of glucose per diem, with a small amount of albumin. Her carbohydrates were limited to 3 ounces of bread; her glycosuria under treatment varied between 40 and 50 grams.

CASE X (patient of Dr. Pothuisje).—Wb., female, aged fifty-nine years. On a strict diet she excreted 40 to 80 grams of sugar daily; only a slight amount of acetone. The results of treatment were negative.

CASE XI.—R., male, aged about thirty years. Miner by occupation. The man was reckless in his habits; diet could not be certified to, though he was confined to bed in the county hospital. When first seen he passed urine to the quantity of about 350 fluid ounces per diem, containing nearly 890 grams of sugar. Nevertheless, he claimed to feel strong and well. There was marked reaction for acetone, and Professor Engle found a maximum of 7 grains of oxybutyric acid in the first few days. Though the amount of urine and quantity of sugar excreted underwent a great diminution under treatment, the latter could not be regarded as successful. In this and the following case a profuse diarrhea was sometimes present. This was probably occasioned by the infusions. On one occasion, following diarrhea, the quantity of urine fell to 38 ounces, but the proportion of sugar rose to over 15 per cent. The man developed thromboses and general dropsy, and he died about two months after abandonment of the observations.

CASE XII.—M. F., male, laborer, aged about forty-two years. Inmate of the county hospital. Not confined to bed. On a general diet he was passing 324 ounces of urine, containing nearly 912 grams of sugar, in twenty-four hours. He was treated with infusions of beef and of "Holadin." The sugar excretion did not fall much below 300 grams per diem. Diarrhea was frequent during the observations. The patient claimed to feel much better for the treatment, but he was discharged as unimproved.

CONCLUSIONS. 1. Evidence has been presented that in a certain proportion of diabetics beyond middle age the metabolism and general symptoms may be improved and the sugar removed from the urine, at least temporarily, through the administration of an infusion of lean meat acidulated with hydrochloric acid.

2. In a single case of youthful diabetes (Case VII), though neither beef infusion nor pancreatic infusion was alone efficacious, when the one followed the other, or a mixture of the two after an interval of some hours, the urine became sugar-free. After the disease had persisted for some months this happy result could no longer be obtained. Nevertheless, the treatment, especially with the beef infusion, seemed to improve the subjective condition of the patient.

3. No good results attended the use of the commercial pancreatic powder employed.

PASSING LEAKAGE OF THE PULMONARY VALVE.*

BY ROBERT D. RUDOLF, M.D., F.R.C.P.,

PROFESSOR OF THERAPEUTICS, UNIVERSITY OF TORONTO; ASSISTANT PHYSICIAN, TORONTO
GENERAL HOSPITAL, TORONTO, CANADA.

INCOMPETENCE of the pulmonary valve due to organic disease is a very rare condition. Only 24 cases were noted at Guy's Hospital out of 16,000 postmortem examinations during a period of thirty-two years,¹ and 3 among 24,000 cases admitted to the medical wards of Johns Hopkins Hospital.² But leakage may occur much more commonly here when the flaps of the valve are normal, but the ring to which they are attached is so dilated that the normal flaps are no longer able to close the enlarged orifice. It is with this latter condition, the so-called relative incompetence, that we are here concerned.

Relative incompetence is a condition not easy to demonstrate post mortem, and many cases, no doubt, occur during life, and have been carefully described, in which the valve was found at the autopsy to be competent. R. B. Preble³ and others have published cases in which post mortem the pulmonary valve was incompetent and would not hold water, and yet the flaps were normal in every way; but it is easy to understand that, as long as any elasticity remains in the structures about the pulmonary orifice, this ring will tend to return to its normal size as soon as the pressure stretching it is removed. Thus, a valve which has leaked freely during life may post mortem appear to be normal, and may even hold water,

* Read by title before the Association of American Physicians, May 10, 1911.